Clinical and Experimental Obstetrics & Gynecology

*Clin. Exp. Obstet. Gynecol.* **2024**; 51(4): 92
https://doi.org/10.31083/j.ceog5104092

*Original Research*

# Association of Pelvic Organ Prolapse and Changes in Bone Imaging Biomarkers in Postmenopausal Women with Low Bone Mineral Density

María Pérez Arguedas[1,*], Ernesto Bas Esteve[2], Alenda Jiménez García[1], Francisco Nohales Alfonso[2], Ana Jimenez-Pastor[3], Luis Martí-Bonmatí[4]

[1]Department of Obstetrics and Gynaecology, Manises Hospital, 46940 Valencia, Spain
[2]Department of Obstetrics and Gynaecology, La Fe Polytechnic and University Hospital, 46026 Valencia, Spain
[3]Quibim (Quantitative Imaging Biomarkers in Medicine), 46021 Valencia, Spain
[4]Department of Radiology, La Fe Polytechnic and University Hospital, 46026 Valencia, Spain
*Correspondence: maria_p_a_22@hotmail.com (María Pérez Arguedas)
Academic Editor: Hiroshi Matsushita
Submitted: 21 December 2023 Revised: 20 February 2024 Accepted: 1 March 2024 Published: 10 April 2024

**Abstract**

**Background**: To test the hypothesis that pelvic organ prolapse (POP) and osteoporosis are both manifestations of a connective tissue disorder, we evaluated whether there is an association between presence of POP and bone imaging biomarkers in postmenopausal women with low bone mineral density (BMD). **Methods**: A blind analytical, observational, and prospective cross-sectional study recruited 89 postmenopausal women with low BMD. Women were divided into those with absent/minimal or with moderate-to-severe POP. An X-ray of the spine was performed followed by a computational image analysis to quantify textural features on each vertebral body. Statistical analysis with a stepwise binary logistic regression model was used. **Results**: After 10 steps, the final model showed significance ($p < 0.05$) in the Omnibus coefficients test. The model classification results were high with over 80% success rates for both groups and an accuracy of 83%. The verification table showed that 39 of the 46 non-prolapsed patients were classified correctly, while 7 women were classified as having prolapsed. Among the 43 patients that had prolapsed, 35 patients were correctly classified while 8 were wrongly classified. The logistic regression analysis confirmed that both groups (prolapsed and non-prolapsed patients) can be differentiated using bone biomarkers on plain films. Most of the significant changes were found on the dorsal vertebrae. **Conclusions**: Pelvic organ prolapse is related to changes in bone imaging biomarkers, besides BMD. These results support the hypothesis that both pelvic prolapse and osteoporosis have a common causal origin.

**Keywords:** pelvic organ prolapse; osteoporosis; collagen metabolism alteration; imaging biomarkers; osteoporotic bone fractures

## 1. Introduction

Pelvic organ prolapse (POP) is the herniation of pelvic organs through the vagina. The prevalence of this condition has been estimated at around 3% in women aged over 20 years [1,2]. In their literature review, Barber and Maher [3] reported that symptomatic POP prevalence increased to 50% after an objective pelvic exam. It is therefore a common pathology, which decreases affected women's quality of life, and is the most frequent indication for gynaecological surgery linked to age [4,5].

The causes of POP are multifactorial, its pathophysiological mechanism being not yet fully understood. Some known (although not sufficient) risk factors are multiparity, old age and overweight [6]. Several studies have reported on the association between changes in the connective tissue and POP [7–9]. Initially, Jackson *et al.* [7] presented a hypothesis involving alterations in pelvic floor connective tissue that attempted to explain the development of POP at the molecular level. This hypothesis was corroborated in subsequent studies [8,10].

Collagen is the most common protein in the human body. Types I, II and V are the main structural components of the vaginal epithelium and endopelvic fascia [9]. Quantitative and qualitative alterations to collagen have been demonstrated in patients with POP through vaginal biopsy [10–12].

Osteoporosis is characterised by low bone mass, altered microarchitecture, and increased skeletal fragility that leads to fractures [13,14]. Although related to age, this disease is also linked to other secondary factors such as hereditary, environmental, iatrogenic, and lifestyle factors. The World Health Organization defines osteoporosis in postmenopausal women as a decrease in the bone mineral density (BMD) in the femoral neck and/or spine with a T-score (measured by dual-energy X-ray absorptiometry) lower than 2.5 standard deviations [15]. Bone quality is not included in the definition.

Other analytical tools, such as the Trabecular Bone Score (TBS), have been used to determine the contribution of bone abnormalities to skeletal fragility. This technique yields information related to trabecular microarchitecture, but the relationship between change in TBS and fracture risk remains to be elucidated [16].

Bone loss originates from an imbalance between bone formation and resorption, with collagen having an impact on bone metabolism [17]. Type I collagen is the most abundant protein in the human body and the principal component of bone. It is the main protein in the extracellular matrix involved in calcification and plays an important role in osteoblast differentiation [18].

Both POP and osteoporosis may be partially explained by an alteration in collagen metabolism, with an association between POP and decreased bone mineral density [19] and a relationship between POP and osteoporotic fractures [8, 20,21]. However, there have been no prospective studies assessing the association between POP and bone quality.

We hypothesize that POP is related to changes in bone quality beyond a decreased BMD, and that this change may be quantified by digital image processing techniques. These changes would predispose patients with POP to a higher risk of osteoporotic fractures.

## 2. Materials and Methods

A blind analytical, observational, and prospective cross-sectional study was designed with the aim of establishing the association between genital prolapse and osteoporosis by measuring bone imaging biomarkers other than BMD.

After approval from the Ethics Committee of our hospital (number 2016/0493), postmenopausal women over 55 years with a BMD indicative of severe osteopenia (T-score <–2) or osteoporosis (T-score <–2.5), of Caucasian and Hispanic ethnicity, were recruited between October 2017 and May 2019.

The exclusion criteria were a history of premature menopause without treatment, symptomatic prolapse diagnosed before menopause, nulliparity, secondary osteoporosis due to diseases or long-term (>3 months) corticosteroid treatment, and patients with current or past treatment for osteoporosis.

We performed 468 densitometric studies (BMD) and selected those cases with a column T-score <–2 (164 cases). All participants signed an informed consent.

Patient were divided into two groups according to the absence or presence of POP, and assessed by an expert gynaecologist with 20 years' experience using the pelvic organ prolapse quantification (POP-Q) system [22]. Prolapse was defined as the descent of any compartment to level II or higher, whether symptomatic or not.

All patients were scheduled for a lateral X-ray of the spine. Each vertebral body from D4 to L5 was segmented manually (itk-SNAP software, University of Pennsylvania, Philadelphia, PA, USA) [23]. The observers were blinded to the patient's group (Fig. 1). Then, from each segmented vertebral body, textural features were computed using the QP Texture® tool (Quibim, Valencia, Spain). Finally, morphological variables such as the antero-posterior and antero-medial ratios were assessed (Fig. 2).

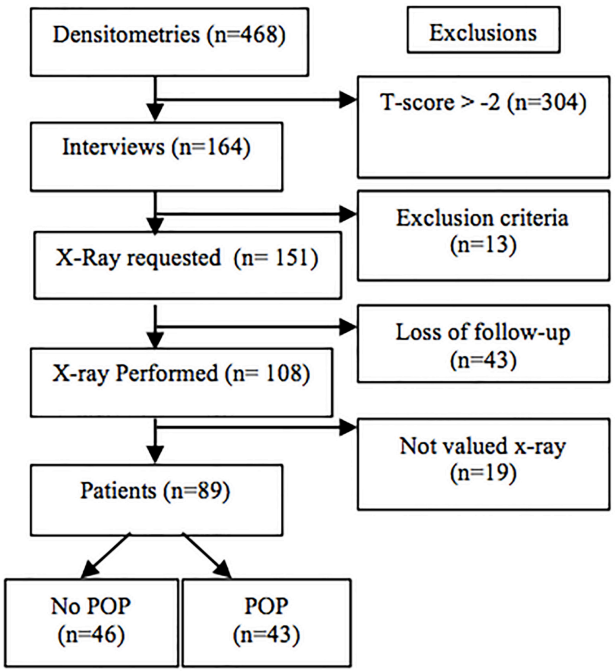


**Fig. 1. Recruitment flowchart.** POP, pelvic organ prolapse.

Textural analysis can be used to obtain descriptors to characterize the structural heterogeneity of vertebral bodies. First-order textural analysis involves extracting features from the histogram of pixel intensities, mainly kurtosis and skewness. Kurtosis provides information on which intensity values of the histogram are more concentrated in the centre and in the tails of the distribution, or whether it is a flatter histogram with smaller tails (Fig. 3). Second-order textural analysis considers the distribution of pixel intensity values in image space. A "Gray level Co-Occurrence Matrix" (GLCM), which is one of the most used applications for textural analysis in radiology [24], was used in the current study.

Nineteen second-order textural features were extracted from the GLCM: autocorrelation, cluster prominence, cluster shade, contrast, correlation, difference entropy, difference variance, dissimilarity, energy, entropy, homogeneity, information measure of correlation 1, information measure of correlation 2, inverse difference, maximum probability, sum average, sum entropy, sum of squares variance, and sum variance. All of these provide information about the heterogeneity of the area under study.

## 3. Results

For the final statistical analysis, we eliminated from the database those patients for whom complete radiological coverage (L1–L5 and D4–D12) was not available. This reduced our database to 89 patients: 46 in the prolapse group and 43 in the non-prolapse group. We performed a descriptive statistical analysis of the population (Table 1), prior to the computational image analysis results.

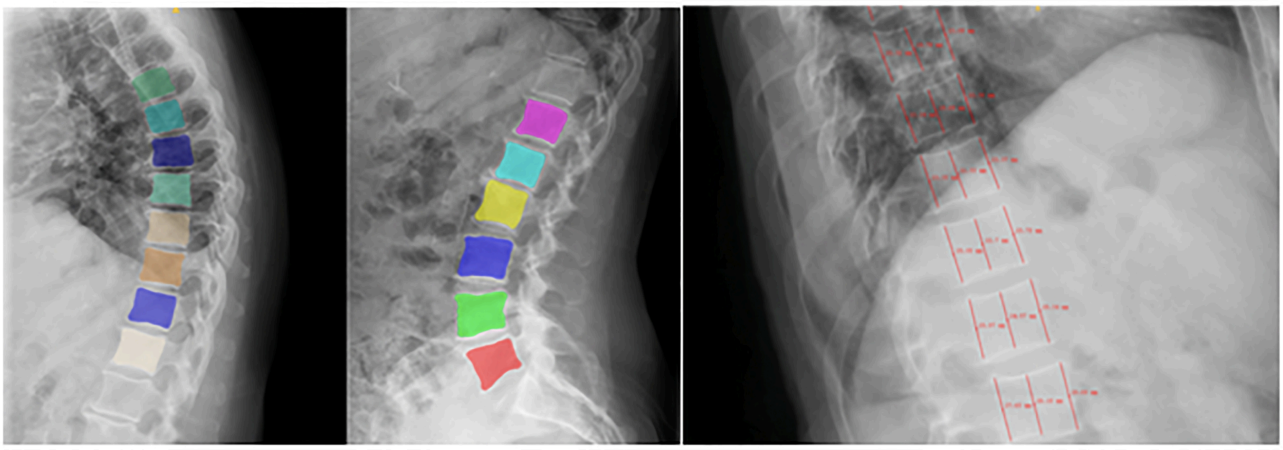

**Fig. 2. Segmentation and measurement of vertebral heights.**

**Table 1. Clinical characteristics of the postmenopausal women (mean ± standard deviation (SD)).**

| | Moderate to severe POP (n = 43) | Absent POP (n = 46) | *p*-value |
|---|---|---|---|
| Age (years) | 68.00 ± 8.34 | 61.91 ± 4.74 | 0.000 |
| Age at menopause (years) | 49.57 ± 3.85 | 50.45 ± 3.38 | 0.000 |
| BMI (kg/m$^2$) | 27.20 ± 4.10 | 25.10 ± 3.54 | 0.012 |
| Vaginal delivery | 2.42 ± 1.23 | 1.69 ± 1.00 | 0.003 |
| Lumbar spine (T-score) | –2.61 ± 0.61 | –2.69 ± 0.54 | 0.428 |
| Femur neck (T-score) | –1.78 ± 0.88 | –1.60 ± 0.54 | 0.298 |
| Smoking (incidence) | 0.04 | 0.34 | 0.023 |
| Familiar fracture (incidence) | 0.11 | 0.19 | 0.179 |
| Personal fracture (incidence) | 0.16 | 0.06 | 0.314 |
| Falling (incidence) | 0.20 | 0.08 | 0.379 |

BMI, body mass index; POP, pelvic organ prolapse.

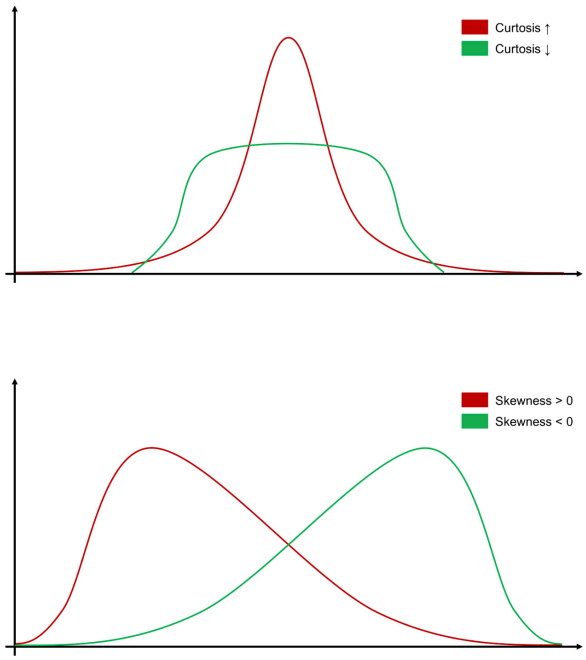


**Fig. 3. Histogram features.**

The database was restructured so that, for each patient, all the variables of each vertebra were considered, instead of considering vertebrae as separate entities.

Due to the high number of variables, and the lack of a theoretical and intuitive basis for choosing which variables were optimal for the model, a "stepwise" logistic regression methodology was chosen; the system automatically chose which were the most significant variables for maximizing the model's classification success.

SPSS V.25 (IBM, Armonk, NY, USA) was used for the statistical analysis. Student's *t* test was performed on the restructured database, obtaining 41 significant variables of the 392 measured ($p < 0.05$). Thirty-nine of these variables (95.1%) were extracted from the dorsal vertebrae, and 37 (90.2%) were related to a specific vertebral group: from D5 to D9. The Student's *t* test showed that there were significant differences in bone imaging biomarkers in the D5–D9 group of vertebrae that were useful for discriminating between the two groups of patients.

Some textural features with statistically significant differences were highly correlated with each other (Fig. 4), and therefore, to control the collinearity between variables, a "stepwise" methodology was conducted for feature selection. We used a binary logistic regression method to dif-

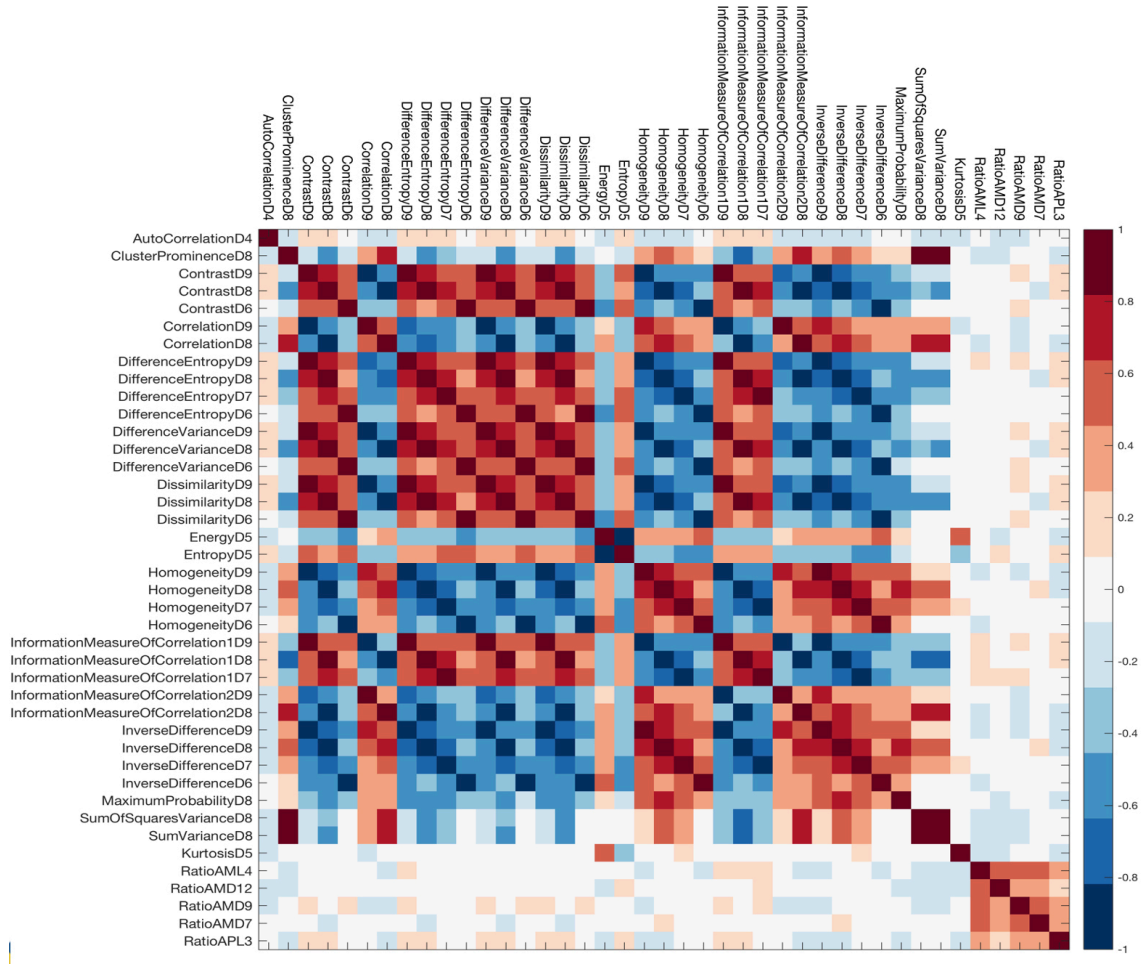


**Fig. 4. Correlation matrix between variables.**

**Table 2. Indicators of the goodness of fit.**

| Omnibus test | Cox and Snell R-squared | Nagelkerke R-squared | Hosmer and Lemeshow test |
|---|---|---|---|
| 0.000 | 0.496 | 0.661 | 0.137 |

ferentiate between prolapse and non-prolapse groups, and after 10 steps we obtained a final model that had a $p$-value $< 0.05$ in the Omnibus coefficients test. The Cox and Snell R-squared and Nagelkerke R-squared analysis yielded unusually high values, which indicated a good fit of the model. The Hosmer and Lemeshow test was another indicator of the goodness of fit, showing non-significant differences ($p > 0.05$) between the predicted probabilities and the ground truth (Table 2). The model classification results were high, as over 80% success rates were obtained from both groups with an accuracy of 83% (Table 3).

**Table 3. Model classification rates.**

| | | Predicted | | Percentage correct |
|---|---|---|---|---|
| | | POP | Non POP | |
| Observed | POP | 39 | 7 | 84.8% |
| | Non POP | 8 | 35 | 81.4% |
| Global percentage | | | | 83.3% |

POP, pelvic organ prolapse.

The verification table showed that 39 of the 46 non-prolapsed patients were classified correctly, while 7 women were classified as having prolapsed. Among the 43 patients that had prolapsed, 35 patients were correctly classified while 8 were wrongly classified. The logistic regression analysis confirmed that both groups (prolapsed and non-prolapsed patients) can be differentiated using bone biomarkers on plain films. Most of the significant changes were found on the dorsal vertebrae.

Once the analysis was complete, 10 variables were included in the model, all of them with a significant Wald statistic ($p < 0.05$) (Table 4). The logistic regression analysis confirmed the results of the Student's $t$ test; most of the changes that allowed discrimination between the groups were located on the dorsal vertebrae (9 of the 10 variables introduced in the model).

**Table 4. Significant Wald statistic of the variables included in the model.**

| Variable | Sig |
|---|---|
| Auto correlation D6 | 0.000 |
| Auto correlation D4 | 0.000 |
| Cluster prominence D9 | 0.005 |
| Difference variance D9 | 0.001 |
| Sum entropy D5 | 0.013 |
| Kurtosis D10 | 0.021 |
| Kurtosis D5 | 0.006 |
| Ratio AM (normal) D7 | 0.004 |
| Ratio AP (normal) D7 | 0.030 |
| Ratio AP (normal) D6 | 0.009 |

AM, anteromedial; AP, anteroposterior.

**Table 5. Variance inflation factor (VIF) measurements.**

| Variable | VIF |
|---|---|
| Auto correlation D6 | 1.293 |
| Auto correlation D4 | 1.329 |
| Cluster prominence D9 | 1.450 |
| Difference variance D9 | 1.443 |
| Sum entropy D5 | 2.852 |
| Kurtosis D10 | 1.455 |
| Kurtosis D5 | 2.651 |
| Ratio AM (normal) D7 | 1.274 |
| Ratio AP (normal) D7 | 1.414 |
| Ratio AP (normal) D6 | 1.608 |

VIF, variance inflation factor; AM, anteromedial; AP, anteroposterior.

VIF (variance inflation factor) measurements were performed to confirm that the selected variables did not suffer high collinearity effects (Table 5) [25]. All the variables in the model had a VIF lower than 10.

## 4. Discussion

Our study confirms that POP is related to changes in bone quality imaging biomarkers besides a low BMD. These objective changes occur more frequently at the dorsal level. Analysis of imaging biomarkers in digital plain films of the spinal column allowed us to differentiate between groups of patients with and without pelvic prolapse. The radiomic changes can be objectively extracted by digital image processing techniques, supporting the hypothesis that both entities have a common causal origin.

Since osteoporosis and POP are a major public health problem, due to their associated morbidity and mortality, the demonstration of a common causal origin may allow a better diagnostic approach and treatment options for both conditions. The fact that most of the spinal changes related to POP are located in the dorsal vertebrae may be related to the predisposition of this area to osteoporotic fractures, since this is the region in which they most frequently appear.

During recent years new theories have emerged suggesting that collagen alteration could play a major role in the development of osteoporosis, given its role in bone metabolism and the maintenance of mechanical resistance. For example, we know that the organin matrix of the bone is constituted mostly by collagen fibres (85–90% of the protein component of the matrix) [19].

The alteration of this collagen fibers explains why many hereditary connective tissue disorders have been associated with fractures [26].

Abnormalities of the connective tissue of the pelvic floor have also been considered an important aetiological factor in genitourinary prolapse given that connective tissue and extracellular matrix components play a vital role in maintaining the normal position of pelvic floor organs. It is been widely demonstrated that congenital weakness of connective tissue due a genetic mutation is a predisposing risk factor for POP [27].

There is evidence of differential gene expressions levels of cartilage oligomeric matrix protein, collagen I, and metalloproteinase-9 between patients with POP and control individuals [28,29]

Jackson's [7] hypothesis, postulated two decades ago, remains valid: the degradation of collagen due to an increase in the metalloproteinase enzyme may take place in young patients with POP.

In the long term, collagen content in the tissue decreases, and in addition, many of its cross-links will be immature, giving rise to new collagen that degrades easily. This negatively impacts mechanical resistance and makes the tissue (bone and tendons, fascias, ligaments and muscles of the pelvic floor) more fragile and susceptible to rupture.

We are aware of some limitations of our study in terms of the size of the database and the classification of populations. This prospective study attempted to reduce bias as much as possible using strict exclusion criteria to avoid having patients with secondary osteoporosis. A larger database would be necessary to verify the significance of the imaging biomarkers. The application of a classic Genant test to the database would be useful to determine whether the objective changes in pixel intensity and texture are translated in osteoporotic bone fractures and could be used in clinical practice. In addition, statistical tools should be used to control the collinearity between variables so we can obtain more reliable results.

In summary, pelvic organ prolapse and bone quality imaging biomarkers, other than BMD, are related, mainly at the dorsal level.

## 5. Conclusions

Our study confirms that pelvic organ prolapse is related to changes in bone imaging biomarkers other than

BMD. These results support the hypothesis that both pelvic prolapse and osteoporosis have a common causal origin.

Studies with a larger sample size are needed to determine whether these results could be used to predict osteoporotic bone fractures.

## Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Author Contributions

All the named authors satisfied the criteria of the ICMJE guidelines. FNA designed the research study. EBE and MPA performed the research. AJG analysed the data. AJP helped with the examination of the textural features. LMB supervised the radiological study, carried out all the radiological studies and helped in the conception of the study. All authors contributed to editorial changes in the manuscript and helped to carry out the study. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the "Instituto de Investigación Sanitaria" of La Fe Polytechnic and University Hospital (approval number: 2016/0493). All subjects gave their informed consent for inclusion before they participated in the study after reading the detailed information form that we provided them.


## Acknowledgment

We would like to express our gratitude to all those who helped us during the writing of this manuscript, especially the members of the skeletal section of the Department of Radiology of La Fe Polytechnic and University Hospital.

## Funding

This research received no external funding.


## Conflict of Interest

The authors declare no conflict of interest. The author Ana Jimenez-Pastor is from Quibim (Quantitative Imaging Biomarkers in Medicine), but Quibim did not participate in the preparation and publication process of the manuscript, and there is no potential conflict of interest.

## References


[1] Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, *et al*. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008; 300: 1311–1316.

[2] Wu JM, Vaughan CP, Goode PS, Redden DT, Burgio KL, Richter HE, *et al*. Prevalence and trends of symptomatic pelvic floor disorders in U.S. women. Obstetrics and Gynecology. 2014; 123: 141–148.

[3] Barber MD, Maher C. Epidemiology and outcome assessment of pelvic organ prolapse. International Urogynecology Journal. 2013; 24: 1783–1790.

[4] Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. Obstetrics and Gynecology Clinics of North America. 1998; 25: 723–746.

[5] Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstetrics and Gynecology. 1997; 89: 501–506.

[6] Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford Family Planning Association Study. British Journal of Obstetrics and Gynaecology. 1997; 104: 579–585.

[7] Jackson SR, Avery NC, Tarlton JF, Eckford SD, Abrams P, Bailey AJ. Changes in metabolism of collagen in genitourinary prolapse. Lancet. 1996; 347: 1658–1661.

[8] Kerkhof MH, Hendriks L, Brölmann HAM. Changes in connective tissue in patients with pelvic organ prolapse–a review of the current literature. International Urogynecology Journal and Pelvic Floor Dysfunction. 2009; 20: 461–474.

[9] Lapiere CM, Nusgens B, Pierard GE. Interaction between collagen type I and type III in conditioning bundles organization. Connective Tissue Research. 1977; 5: 21–29.

[10] Chen B, Yeh J. Alterations in connective tissue metabolism in stress incontinence and prolapse. The Journal of Urology. 2011; 186: 1768–1772.

[11] Moalli PA, Shand SH, Zyczynski HM, Gordy SC, Meyn LA. Remodeling of vaginal connective tissue in patients with prolapse. Obstetrics and Gynecology. 2005; 106: 953–963.

[12] Lin SY, Tee YT, Ng SC, Chang H, Lin P, Chen GD. Changes in the extracellular matrix in the anterior vagina of women with or without prolapse. International Urogynecology Journal and Pelvic Floor Dysfunction. 2007; 18: 43–48.

[13] Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, *et al*. UK clinical guideline for the prevention and treatment of osteoporosis. Archives of Osteoporosis. 2017; 12: 43.

[14] Herrera A, Martínez AA, Ferrandez L, Gil E, Moreno A. Epidemiology of osteoporotic hip fractures in Spain. International Orthopaedics. 2006; 30: 11–14.

[15] Boonen S, Singer AJ. Osteoporosis management: impact of fracture type on cost and quality of life in patients at risk for fracture I. Current Medical Research and Opinion. 2008; 24: 1781–1788.

[16] Harvey NC, Glüer CC, Binkley N, McCloskey EV, Brandi ML, Cooper C, *et al*. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone. 2015; 78: 216–224.

[17] Nomura Y, Oohashi K, Watanabe M, Kasugai S. Increase in bone mineral density through oral administration of shark gelatin to ovariectomized rats. Nutrition. 2005; 21: 1120–1126.

[18] Takeuchi Y, Nakayama K, Matsumoto T. Differentiation and cell surface expression of transforming growth factor-beta receptors are regulated by interaction with matrix collagen in murine osteoblastic cells. The Journal of Biological Chemistry. 1996; 271: 3938–3944.

[19] Lee SW, Cho HH, Kim MR, You YO, Kim SY, Hwang YB, *et al*. Association between pelvic organ prolapse and bone mineral density in postmenopausal women. Journal of Obstetrics and Gynaecology. 2015; 35: 476–480.

[20] Pal L, Hailpern SM, Santoro NF, Freeman R, Barad D, Kipersztok S, *et al*. Association of pelvic organ prolapse and fractures in postmenopausal women: analysis of baseline data from

the Women's Health Initiative Estrogen Plus Progestin trial. Menopause. 2008; 15: 59–66.

[21] Melton LJ, 3rd, Achenbach SJ, Gebhart JB, Babalola EO, Atkinson EJ, Bharucha AE. Influence of hysterectomy on long-term fracture risk. Fertility and Sterility. 2007; 88: 156–162.

[22] Persu C, Chapple CR, Cauni V, Gutue S, Geavlete P. Pelvic Organ Prolapse Quantification System (POP-Q) - a new era in pelvic prolapse staging. Journal of Medicine and Life. 2011; 4: 75–81.

[23] Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, *et al*. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. NeuroImage. 2006; 31: 1116–1128.

[24] Haralick RM, Shanmugam K, Dinstein IH. Textural features for image classification. IEEE Transactions on Systems, Man, and Cybernetics. 1973; 610–621.

[25] Kleinbaum, DG, Kupper LL, Nizam A, Muller KE. Applied regression analysis and other multivariable methods. Duxbury press: Belmont, CA. 1988.

[26] Charoenngam N, Rittiphairoj T, Jaroenlapnopparat A, Ponvilawan B, Waitayangkoon P, Supakitjanusant P, *et al*. THU411 Fracture and Osteoporosis in Hereditary Connective Tissue Disorders: A Systematic Review And Meta-analysis. Journal of The Endocrine Society. 2023; 7: bvad114.372.

[27] Laktionova MV, Aringazina AM, Kulzhanov MK, Baimuratova MA, Askerov AA, Khamidullina ZG. Epidemiology, etiology and prevention of genital prolapse. Science & Healthcare. 2023; 25: 247–256.

[28] Widayana KA, Putra IGM, Megadhana IW, Suwardewa TGA, Mahendra INB, Wiradnyana AAGP, *et al*. The Matrix Metalloproteinase-9 Gene Polymorphisms as Risk Factor for Pelvic Organ Prolapse in Balinese Women. Journal of South Asian Federation of Obstetrics and Gynaecology. 2023; 15: 65–70.

[29] Chen YF, Xu HN, Duan YN, Xia ZJ. Altered Expression of COMP, Collagen 1, and MMP9 in Pelvic Organ Prolapse. Biomedical and Environmental Sciences. 2023; 36: 979–982.